at the household level with an agent-based mathematical model and investigated the effects of various case management rates, maintenance of vector control, features of reactive case detection programs, and larger-scale drug- and insecticide-based responses on outbreak management and prevention of resurgence in three representative communities in southern Zambia. We find that excellent surveillance is a necessary condition for preventing reestablishment, and we predict that many areas of sub-Saharan Africa will require continued refreshing of vector control until elimination is achieved on a broader regional scale and importation becomes unlikely. The intensity of reactive activities needed to maintain elimination varies with both local receptivity and local configuration of households, with densely populated areas requiring larger radius of follow-up activities. Since asymptomatic infections remain likely when infections are imported into areas with substantial lingering immunity, adaptive responses where mass drug campaigns are triggered when clinical case counts surpass a pre-determined threshold can be a powerful tool for managing outbreaks. These results suggest a general set of guidelines for programs seeking to maintain elimination in areas that remain vulnerable to importation pressure.

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DEVELOPING A NATIONAL MALARIA ELIMINATION INVESTMENT CASE: A FRAMEWORK AND APPLICATION

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The World Health Organization's *Global Technical Strategy for Malaria 2016-2030* calls for malaria elimination in at least 35 countries by 2030. To achieve this ambitious target, national malaria programs will require adequate financial resources to interrupt local transmission and prevent reintroduction. Donor funding for malaria elimination, however, has decreased in recent years, and competing priorities, coupled with a low priority given to malaria as a result of reduced transmission rates, often lead governments to withdraw funding for malaria at a critical juncture. Historical evidence suggests that ill-timed downsizing of malaria programs can lead to deadly and costly resurgences. To sustain political and financial commitment, policymakers responsible for resource allocation must be convinced of the economic returns of eliminating malaria. An investment case can present the rationale for investing in clear and concise terms. Building on existing literature, we developed a framework for national malaria elimination investment cases. The framework has four sections, namely (1) proposed investment, (2) rationale for investing, (3) financial landscape, and (4) issues to consider. The framework, when properly adapted, can help malaria programs gather and generate evidence on the costs, benefits, risks, and financial viability of national malaria elimination. We applied this framework to Papua New Guinea, a malaria endemic country that has aligned itself with the regional goal of making Asia Pacific malaria-free by 2030. Using the outputs of a dynamic transmission model, we estimated the total cost of eliminating malaria to be US$454 million (range: US$282-701 million) in 2016-2030, or $30 million on average per year. This is roughly US$14 million more than what was spent on malaria control in 2015. Elimination by 2030 can save over 14,500 lives and avert over 7.8 million cases. The net economic benefits of elimination compared to a business-as-usual scenario is roughly US$5 billion (range: US$4-7 billion). The median return on investment is 17, indicating that the incremental costs of elimination greatly outweigh its costs.

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HIGH LEVEL EFFICACY IN HUMANS OF A NEXT-GENERATION *PLASMODIUM FALCIPARUM* ANTI-SPOROZOITE VACCINE: R21 IN MATRIX-M™ ADJUVANT

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It remains a global health priority to develop a durable and highly efficacious malaria vaccine. The most advanced malaria vaccine candidate, RTS,S/AS01 has completed Phase III testing in a multicentre study across several African sites and demonstrates low-level (~30%) efficacy against clinical malaria in children aged 5-17 months after a three dose schedule. Efficacy wanes rapidly over time and there remain some safety concerns that require further assessment in the planned pilot deployment trials due to commence in Africa in 2018. There is a need to improve on RTS,S/AS01 to achieve WHO development goals of a durable vaccine with >75% efficacy. RTS,S comprises recombinant particles expressing the central repeat and the C-terminus of the circumsporozoite protein (CSP) fused to Hepatitis B surface antigen (HBsAg). R21 has been developed at the Jenner Institute, University of Oxford. This is an improved HBsAg-CSP-based construct, but without any unfused HBsAg protein which is present at a four-fold molar excess in RTS,S particles. This excess of HBsAg was required for RTS,S to form a particle; however, R21 forms particles without excess HBsAg by utilizing the better expressing yeast, *Pichia pastoris*. Matrix-M (MM) is a promising, novel saponin-based adjuvant that has been tested safely with vaccines for a number of diseases in over 1000 subjects. We previously showed that R21 administered with MM is safe and has comparable immunogenicity at much lower doses compared to RTS,S/AS01: 10µg doses of R21/MM induced the same antibody titres to the CSP repeat as 50µg of RTS,S/AS01B. Durable humoral responses at 6 months were higher for the 10µg than the 50µg dose of R21/MM. We report a Phase IIa efficacy trial using controlled human malaria infection in healthy UK adult volunteers. Three doses of 10µg R21 adjuvanted with MM given 4 weeks apart demonstrated high level sterile efficacy [(81.8%; n=11); p=0.0009]. Furthermore, we observed significantly reduced reactogenicity compared to reported data on the standard RTS,S/AS01 regimen. These data provide strong support for this R21/MM vaccine to be evaluated further in African adults, children and infants.

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SAFETY AND IMMUNOGENICITY OF THE NOVEL *PLASMODIUM FALCIPARUM* BLOOD-STAGE VACCINE RH5.1/AS01B IN A PHASE I/IIA CLINICAL TRIAL

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The development of an effective blood-stage malaria vaccine holds significant promise, not only for reducing the morbidity and mortality associated with malaria, but also for reducing transmission, either alone or as a crucial component of a multi-stage vaccine. The reticulocyte-binding protein homologue 5 (RH5) is the most promising blood-stage *P. falciparum* candidate antigen to date. It is essential for parasite survival and erythrocyte invasion, has limited polymorphism, and antibodies induced by RH5 in preclinical *in vitro* studies overcome two of the long-standing difficulties associated with other merozoite antigens: first, they can block erythrocyte invasion to high efficiency (requiring lower antibody concentrations); and second, cross-inhibit all *P. falciparum* lines and field isolates tested to-date. Efficacy has been shown against a stringent heterologous strain blood-stage challenge in an *in vivo Aotus* monkey-*P. falciparum* challenge model, following vaccination with RH5 protein. Protection was strongly correlated with anti-RH5 serum IgG antibody concentration and *in vitro* functional growth inhibition activity (GIA). Here we report on a first-in-human Phase Ia clinical trial (NCT02927145) of the recombinant protein RH5.1 delivered with GSK's adjuvant AS01B to 48 healthy, malaria-naïve UK adult volunteers (four groups of n=12). Group 1 receive a lead-in dose (2 µg) of RH5.1 (given 3 times 4 weeks apart) before dose escalation to 10 µg in Group 2, and then 50 µg in Group 4 (same schedule). Group 3 receive 50 µg twice 4 weeks apart followed by a delayed, fractional dose (10 µg) boost at 6 months. All groups receive the same dose (0.5 mL) of AS01B. This is the first RH5 protein/adjuvant vaccine to be tested in humans. The vaccine is well tolerated at all doses. There have been no safety concerns and no SAEs to-date. T cell, B cell and serum antibody responses have been assessed by ELISpot, flow cytometry and quantitative ELISA and purified IgG is tested for anti-parasitic function using the *in vitro* GIA assay. These promising data will be presented and RH5.1/AS01B will be tested for efficacy in a Phase IIa blood-stage CHMI trial in late 2017.

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INTEGRATED ANALYSIS OF ANTIBODY, CYTOKINE AND T CELL RESPONSES INDUCED BY RTS,S/AS01E VACCINATION WITHIN THE AFRICAN PEDIATRIC PHASE 3 TRIAL: SEARCHING FOR CORRELATES OF PROTECTION

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The RTS,S/AS01E malaria vaccine is the most clinically advanced, however there is still a need to better characterize and integrate antibody and cellular immune responses elicited upon vaccination to understand its moderate and short-lasting protection. We assessed the antibody and cellular responses to the RTS,S/AS01E antigens circumsporozoite protein (CSP) and Hepatitis B surface antigen (HBsAg) at baseline and one month post primary vaccination by luminex and intracellular cytokine staining and flow cytometry in RTS,S-vaccinated and control-vaccinated children recruited in two of the African sites of the phase III trial: Manhiça (Mozambique) and Bagamoyo (Tanzania). We aimed to explore the association between antibody and cellular responses induced by the vaccine, focusing on specific cell types and cytokines of the T helper phenotype. RTS,S vaccination induced polyfunctional CSP- and HBsAg-specific CD4+ T cells and antibodies of different isotypes/subclasses and degrees of avidity to multiple CSP B cell epitopes (NANP, C-terminal and full lenght). RTS,S-vaccinated children had significantly higher frequencies of CSP- and HBsAg-specific CD4+ T cells producing IL-2, TNF-α and CD40L and HBsAg-specific CD4+ T producing IFN-γ and IL-17 than controls or baseline frequencies; these responses were confined in central and effector memory compartments. Additionally, effector memory CD4+ T cells producing IL-4 and IL-21 were detected for both vaccine antigens. Furthermore, we identified distinct profiles of antigen-specific cytokine responses associated with RTS,S vaccination and protection/risk of malaria. We will present data on the correlation between such cytokine profiles and antibody responses induced by the vaccine in African children. Data thus far show that RTS,S/AS01E vaccine induces antibody and T cell responses of higher quality and complexity than previously thought. The joint analysis of responses detected in memory CD4+ T and B cell compartments may provide better correlates of RTS,S/AS01-induced immunity and duration of protection that may guide development of second generation improved candidates.

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IGG PROTEOMICS AND BCR SEQUENCING OF SPECIFIC B CELLS FOR ANTIBODY REPERTOIRE ASSESSMENT AFTER MALARIA TRANSMISSION BLOCKING VACCINATION IN MALIAN ADULTS

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Transmission blocking vaccines induce antibodies that target sexual-stage antigens expressed by the parasite in the mosquito. Antibodies against Pfs25 and Pfs230, molecules present on the surface of the sexual stages of *Plasmodium falciparum,* can reduce parasite burden in the mosquito. Antibody repertoire analyses, performed by BCR sequencing and/or proteomics of serum IgG, have been employed to evaluate vaccine responses. Here, we used a Pfs25 tetramer to sort Pfs25-specific single B cells (Pfs25+, CD3-, CD19+, CD20+) generated after a fourth dose of Pfs25-EPA immunization in Malian adults, and sequenced light and heavy chain of antibody from these cells. In a second approach, Pfs25-specific antibodies were affinity-purified from plasma of vaccinees and analysed by mass spectrometry. For peptide analysis, we used an *in-house* database, generated by immunosequencing a 130-nt fragment of the CDR3 region of the IgH from PBMCs from the same donors. We compared two groups of samples: those with antibodies able to reduce parasite burden in the midgut of a mosquito; and those without such antibody activity. For both groups, we compared IgG sequence alignment/coverage using the PBMC immunosequencing database, CDR3 length, and post-translational modifications. Our results showed that all Pfs25-IgG samples from the high antibody activity group yielded peptides matching CDR3 region sequences generated from study PBMC. Coverages higher than 75% were found only in the high antibody activity group. Hexose was found as post-translational modification only in peptide sequences from the high antibody activity group, suggesting a glycosylation process. CDR3 length did not differ between high and low activity groups. These preliminary analyses demonstrate that proteomics techniques can detect specific IgGs from the vaccine trial. For the BCR sequencing of antigen-specific